Associations between smoking and extra-axial manifestations and disease severity in axial spondyloarthritis: results from the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS)

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Abstract

Objective. The effects of smoking on disease manifestations in axial spondyloarthritis (axSpA) are inadequately described. Utilising a large and well-characterised cohort, we investigated the association between smoking and (i) extra-axial manifestations (EAM) and (ii) disease severity measures.

Methods. Baseline data from the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis were explored. Our analyses focused on EAMs and other disease severity measures, including scales for fatigue, sleep, anxiety and depression. Logistic and linear models were used to quantify associations between disease characteristics according to smoking status (current/ex/never) and quantity (heavy/light), adjusting for age, gender, BMI, education, deprivation, comorbidities, symptom duration and alcohol status.

Results. A total of 2031 participants were eligible for the current analysis (68% male, mean age 49 years). 24% were current and 32% ex-smokers. When compared to non-smokers, current smokers had lower odds of uveitis (OR_{adj} 0.7, 95%CI 0.5 to 0.9) and higher odds of psoriasis (OR_{adj} 1.6, 95%CI 1.1 to 2.3). Ex- and current smokers had incrementally more severe disease than never smokers, with higher BASDAI (β=0.3, 95%CI 0.1 to 0.6; β=0.9, 95%CI 0.6 to 1.2) and BASFI (β=0.5, 95%CI 0.2 to 0.8; β=1.3, 95%CI 1.0 to 1.6); similar associations were observed for fatigue, sleep, anxiety and depression.

Conclusions. In this large cross-sectional study, we observed that smoking is independently associated with an adverse disease profile in axSpA, including worse fatigue, sleep, anxiety, depression and higher odds of psoriasis. The paradoxical association between current smoking and reduced odds of uveitis is interesting and warrants further investigation.

Keywords. Axial spondyloarthritis, ankylosing spondylitis, smoking, uveitis, extra-axial manifestations, registry, fatigue, sleep, psoriasis, depression.

Key messages:

- Baseline smoking status was independently associated with worse disease in axial spondyloarthritis.

- Smoking was associated with an adverse disease profile, including worse fatigue, sleep, anxiety and depression.

- Current smoking was associated with higher odds of psoriasis but, paradoxically, lower odds of uveitis.

Background

The prevalence of cigarette smoking in axial spondyloarthritis (axSpA) is high in the UK with nearly half of patients reporting either current or prior smoking [1-3]. Smoking is associated with earlier symptom onset and worse disease activity, functional impairment and quality of life [4, 5]. Among smokers, there is evidence of an exposure-response relationship: less severe disease is observed with smoking cessation [1] and with lower cumulative pack-year exposure [3]. In longitudinal analyses, smokers were less likely to adhere and respond to TNF inhibition (TNFi) therapy [6].

However, the causal relationship between smoking and axSpA severity is complex. Smoking is frequently associated with socioeconomic factors, health related behaviours and comorbidity. It is essential to adjust for these factors when exploring whether smoking has independent effects on the disease and is therefore a potentially modifiable risk factor that could improve outcomes.

There has been no focused analysis of smoking and extra axial manifestations (EAM). Up to quarter of axSpA patients have acute anterior uveitis (AAU) and a similar proportion have peripheral joint involvement, whilst 9% and 7% of patients have psoriasis and inflammatory bowel disease (IBD), respectively [7, 8]. These EAMs can influence treatment, impact allocation of health resources and affect prognosis [7, 9, 10]; exploring their association with smoking is therefore of clinical relevance. Although AAU, psoriasis and IBD are each known to be associated with smoking as independent disease entities [11-13], these associations have not been examined in the context of axSpA. In addition, associations between smoking and several important disease related outcomes have not yet been described, such as fatigue, sleep, anxiety and depression that form key components of holistic care.

Our aim was to use a large and well-characterised national axSpA register to provide an improved description of the associations between smoking and (i) extra-axial manifestations including AAU, psoriasis, IBD, dactylitis, peripheral arthritis and enthesitis, and (ii) other disease severity measures, including fatigue, sleep, anxiety and depression.

Methods

The British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS) is a UK-wide prospective cohort study of axSpA patients fulfilling the ASAS criteria for axial SpA. The study protocol has been previously published [14]. This analysis focused on baseline cross-sectional data before any exposure to biologic therapy, from December 2012 to June 2017. Participants were included in this analysis if they completed the smoking status question of the questionnaire.

Data were obtained from patient completed questionnaires and extracted from medical records by participating centres. Clinical data at the time of recruitment included: all components of ASAS and modified New York criteria [15, 16], symptom duration and body mass index (BMI). A targeted medical history included extra-axial manifestations (EAM) and use of NSAIDs or DMARDs in the past six months. Physician-confirmed diagnoses of AAU, psoriasis and IBD were used, whilst peripheral arthritis, dactylitis and enthesitis were derived from each participant's clinical record. A list of comorbidities was also obtained from clinical records [14]. The number of comorbidities were added and categorised as 0, 1, 2 or ≥3.

Participant questionnaires captured smoking status as never, ex- or current smokers at baseline. Ex- and current smokers were asked their frequency of smoking in the past three months; ex-smokers were defined as those who had not smoked in this period. Current smokers reported average number of cigarettes smoked per day, and were grouped as light smokers (≤10 cigarettes/day, the median quantity) or heavy smokers (>10 cig/day). Alcohol exposure was categorised as current, ex- or never drinkers. Socioeconomic status was approximated using post-code derived Index of Multiple Deprivation (IMD) for each country of the UK, with quintile 1 representing the top 20% most deprived areas and quintile 5 the least deprived [17, 18].

Disease activity was assessed using the Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS), spinal pain visual analogue scale, CRP (mg/dl) and ESR (mm/hr); functional impairment using Bath AS Functional (BASFI) and Metrology Indices (BASMI); quality of life using AS quality of life questionnaire (ASQoL) and EuroQoL (EQ-5D and EQ-VAS) [19]. Additional measures included the Bath AS Global Score (BASG), Chalder Fatigue Scale Likert scale (CFQ) [20], Jenkins Sleep Evaluation Questionnaire [21] and the Hospital Anxiety and Depression Scale (HADS) [22]. Properties of these measures are described in [23, 24] or their respective references; they are collectively referred to as measures of disease severity throughout the text.

Ethical approval was obtained from the National Research Ethics Service Committee North East—County Durham and Tees Valley (reference 11/NE/0374) and informed consent was obtained from all participants.

<u>Analysis</u>

Descriptive statistics were used to compare participant and disease characteristics (measures of disease severity and proportions of EAMs) according to smoking status (current, ex- and never) and quantity (heavy vs light among current smokers).

Logistic and linear models were generated for each EAM and each measure of disease severity, as dependent variables, respectively. The independent variables of interest were (i) smoking status and (ii) smoking quantity. First, models were adjusted for potential confounders (age, gender, BMI, education and IMD). Models were then additionally adjusted for the number of comorbidities, symptom duration and alcohol use. These variables were considered separately since their roles as confounders are less clear: smoking causes several comorbidities and is associated with earlier symptom onset, making these variables potential mediators. Alcohol use is associated with disease activity [25] but it is unclear whether as a cause or consequence.

Interaction terms between smoking and all other covariates were tested. IMD, education, number of comorbidities and alcohol status were entered into models as dummy variables. Smoking status was entered as a dummy variable, which allowed pairwise comparisons to be derived from a single model by changing the reference group: first with never smokers as the reference group (for current/never and ex-/never comparisons), then with ex-smokers as reference group (for current/ex- comparison; never/ex- comparison was omitted). CRP and ESR were transformed using ln(CRP+1) and ln(ESR). No correction was made for multiple comparisons, since many disease severity measures are closely related constructs and their analysis do not constitute completely independent tests.

<u>Sensitivity analyses</u>

Dichotomisation of smoking quantity was arbitrary; therefore we repeated regression models with cigarettes per day as a continuous independent variable. Not all participants responded to smoking questions. To address potential nonparticipation bias, all models were weighted for the inverse of the sampling fraction, where responder and non-responder characteristics were different. This allows data from under-represented groups to be weighted more heavily in the models. All analyses were performed using Stata version 13.

Results

Among a total of 2420 participants with baseline data, 2031 (84%) reported smoking status and formed the cohort for analysis. This cohort was mostly male (68%) with mean age of 49.0 years (SD 14.5). The median symptom duration was 20 years. Criteria for AS was fulfilled by 1431 (70%) and ASAS imaging criteria for axSpA by 1824 (90%). HLA-B27 status was available for 74% participants and was positive in 79% of these cases. The mean BMI was 27.7kg/m^2. 76% reported current alcohol use, 17% previous and 7% never. Current smoking was reported by 490 (24%) participants and previous smoking by 652 (32%), whilst 889 (44%) had never smoked. Among current smokers, 199 (55%) were light smokers and 166 (45%) heavy.

AAU was diagnosed in 483 (24%) participants, psoriasis in 233 (12%) and IBD in 216 (11%). A history of peripheral arthritis was recorded for 794 (41%) participants, dactylitis for 169 (9%) and enthesitis for 470 (24%). At least one comorbidity was present in 875 (44%) participants: hypertension was recorded in 377 (19%) participants, 312 (16%) had depression, 195 (10%) asthma, 94 (4.7%) diabetes, 79 (4.2%) cancer, 65 (3.2%) peptic ulcer, 40 (2.0%) myocardial infarction, 35 (1.7%) renal disease, 33 (1.6%) chronic bronchitis/emphysema, 28 (1.4%) unstable angina, 27 (1.3%) stroke, 20 (1.0%) heart failure and 15 (0.8%) liver disease.

Participant characteristics compared between smoking status/quantity

Table 1 compares participant characteristics between current, ex- and never smokers, and between heavy and light smokers. Never smokers were more likely to be female than current or ex-smokers. Never smokers also showed trends for having higher educational attainment, lower deprivation and fewer comorbidities.

Ex-smokers were the oldest group with longest symptom duration. They had higher prevalence of radiographic sacroiliitis and, as a result, were more likely to meet criteria for AS. Current smokers were less likely to be current alcohol drinkers. They were less likely to meet the ASAS criteria "good response to NSAIDs" but were more likely to have "elevated CRP." Current smokers were less likely to be current drinkers than ex- or never smokers.

Heavy smokers (>10 cigarettes/day) were older and had higher BMI than light smokers (≤10). All other characteristics were similar between heavy and light smokers.

Extra-axial manifestations and smoking status/quantity

Proportions of each EAM for current, ex- and never smokers are shown in Table 2. Adjusting for confounders, current smokers had 32% and 30% lower odds of AAU than either never (OR$_{adj}$ 0.68;

95%CI 0.49 to 0.94) or ex-smokers (OR$_{adj}$ 0.70; 95%CI 0.50 to 0.99), respectively (Table 3). Current smokers had 56% and 66% higher odds of psoriasis than never (OR$_{adj}$ 1.56; 95%CI 1.05 to 2.32) or ex-smokers (OR$_{adj}$ 1.66; 95%CI 1.09 to 2.54), respectively. Ex-smokers were 40% more likely to have a history of IBD, although this was not statistically significant (OR$_{adj}$ 1.40; 95%CI 0.96 to 2.03). There were no significant differences in other EAMs.

Proportions of EAMs were not statistically different between heavy and light smokers in unadjusted (Table 2) or adjusted (Supplementary table 1) comparisons.

Measures of disease severity and smoking status/quantity

A selection of disease severity measures according to each smoking categorisation are shown in Table 2; other disease severity measures are shown in supplementary table 2. All measures were significantly different between current, ex- and never smokers, except ESR. Table 3 and supplementary table 3 show the differences between categories of smoking status from fully adjusted regression models. Results from partially adjusted models are shown in Supplementary table 4. Current smokers had more severe disease than never smokers in terms of disease activity (0.9 units higher BASDAI, 0.5 units higher ASDAS) and functional impairment (1.3 units higher BASFI, 0.6 units higher BASMI). Compared to never smokers, current smokers also reported worse quality of life (ASQoL higher by 2.6 units), fatigue (higher by 1.3 units), sleep (higher by 0.8 units) and anxiety and depression (1.9 units higher for both sub-scores). CRP was higher in current than never smokers but ESR was not.

When current smokers were compared with ex-smokers, effect sizes were smaller than above comparisons but nevertheless significant. Current smokers had worse disease activity (0.6 units higher BASDAI), functional impairment (0.8 units higher BASFI) and depression (1.3 units higher). Current smokers also had higher CRP than those who had quit.

Differences in measures of disease severity were smaller between ex- and never smokers than the above comparisons. Previously observed differences in CRP and EQ5D were no longer significant between ex- and never smokers.

Heavy smokers had worse function (BASFI and BASMI) than light smokers (Table 2 and supplementary table 2). However, the differences were not statistically significant in adjusted models (Supplementary table 1).

Sensitivity analyses

Regression models exploring the association between smoking quantity (in units of 5 cigarettes per day) and EAMs and other measures of disease severity remained non-significant (supplementary table 1). Smoking data was missing for 16% of the cohort; among these 72% had missing questionnaires. Participants with smoking data were older (mean age 49.0 vs 43.6 years, P<0.001) with longer symptom duration (median 20.0 vs 14.8 years, P<0.001) than non-responders. There was also trend to suggest that responders were less deprived and had more comorbidities. All other participant characteristics were statistically similar (supplementary table 5). Applying inverse sampling weights derived from these variables did not significantly change effect estimates (Supplementary table 6).

Interactions between gender and smoking status/quantity

The only significant interaction was between gender and smoking status. Current smokers of both genders had worse disease than never smokers. However, the difference between current and ex-smokers were more consistently observed in males. In females, the effect sizes for AAU (OR_{adj} 0.53; 05%CI 0.29 to 0.97) and psoriasis (OR_{adj} 2.48; 95%CI 1.28 to 4.81) were larger, although differences between the sexes were not statistically significant (supplementary table 6). There were no significant interactions between gender and smoking quantity (results not shown).

Discussion

In this large national cross-sectional study, we found that current smoking was associated with higher odds of psoriasis and, intriguingly, around 30% lower odds of AAU than either ex- or never smokers. We also observed that previous and current smoking exposures were independently associated with incrementally more severe axSpA disease compared to never smoking; this included worse fatigue, sleep, anxiety and depression. These associations remained statistically and clinically significant despite adjusting for important confounders.

A major strength of this study was the quality of data available from the largest cross-sectional cohort to date. This allowed the potential effects of smoking to be quantified in detail and for adjustment for important confounding variables. Participants were recruited from both specialist and non-specialist secondary care centres, thus providing a relatively unselected population. Furthermore, this biologic naïve cohort allowed disease severity to be assessed independent of TNF inhibition therapy.

This observational study used data from an established cohort. Whilst smoking has been recorded in detail, information on pack-years and time since smoking cessation were not recorded. This impacts our interpretation of results and may also explain the lack of associations between smoking quantity and disease severity seen in previous studies using pack-years [3]. These cross-sectional effect sizes were large and should be interpreted with caution; those with more severe disease may also alter their smoking behaviour. The effect of smoking on treatment response was more subtle in longitudinal studies [26, 27]. However, effect sizes in our study were consistent with existing cross-sectional studies [1, 3, 5] and may be clinically important given that ≥2-unit improvement in BASDAI is considered as response to TNF inhibition therapy. The median BASDAI of this cohort was high, but similar to other cross-sectional cohorts [3, 4].

The limitation for causation applies particularly to the counterintuitive finding between smoking and AAU. This association had been observed previously [1, 3, 28]. A proposed explanation was that irritation from cigarette smoke cause patients with AAU to change their behaviour and to stop smoking. However, AAU attacks are typically paroxysmal, with long periods of remission in between. It is therefore less likely to influence permanent lifestyle change than persistent disease features, such as psoriasis. This study is the first to show that never smokers also had higher odds of AAU than current smokers, adjusting for symptom duration. It could also be argued that patients with AAU would avoid smoking altogether. However, the majority of regular smoking starts before 18 years of age in Europe [29]; this is likely to precede the first attack of AAU, the risk of which increases with

longer symptom duration [7]. Studying the relationship between smoking and AAU within a population of axSpA patients effectively conditions on a potential collider (a common effect of smoking and unmeasured confounders between axSpA and uveitis). Such selection bias can induce paradoxical associations between smoking and AAU; for example smoking increases risk of psoriatic arthritis in the general population, but reduces its risk among those with psoriasis [30]. Further exploration of smoking and axSpA-associated AAU is warranted to establish whether this is a statistical or biological phenomenon: A similar lack of smokers had been observed among patients with ulcerative colitis (UC), a condition in which AAU is the most prevalent extra-intestinal feature [31]. Increased risk of UC in both ex- and never smokers is now accepted, although the mechanism remains unclear [12].

The associations between smoking and disease severity are likely explained, at least in part, by the inflammatory effects of smoke inhalation: current smokers had higher CRP. This systemic inflammatory burden may exacerbate the localised disease process in axSpA, as supported by more current smokers having active inflammation on MRI. Interestingly, the prevalence of current smoking in this axSpA cohort is higher than that previously reported in the equivalent UK register for RA (21%) – a disease with greater aetiological links to smoking [32]. Smoking in axSpA may cause additional inflammatory burden that contributes to the development of more extensive inflammatory lesions that can be detected on MRI.

Our results also suggest that some covariates may mediate some of smoking's effect on disease severity, indicated by the reduced effect sizes in fully adjusted models. The fact that these associations with smoking persist despite adjusting for potential mediators supports the hypothesis that smoking has an important direct effect on disease severity. The cross-sectional nature of this study precluded formal mediation analysis, which should be a focus of future longitudinal studies. The interaction between gender and smoking was interesting. However, these findings should be interpreted cautiously, since they were not generated from an a priori hypothesis.

Summary

Using a large and well-characterised national cohort of patients with axSpA, we provide clear evidence that previous and current smoking are associated with incrementally worse disease across a wide range of severity measures. We also found that current smoking was associated with higher odds of psoriasis and lower odds of AAU than either ex- or never smokers. The latter novel finding warrants longitudinal investigation.

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Table 1. Differences in patient and disease characteristics according to smoking status and quantity.		Smoking status				Smoking quantity[+]		
		Never smoker (n=890)	Ex-smoker (n=652)	Current smoker (n=489)	P-value	Light smoker (n=199)	Heavy smoker (n=166)	P-value
Age, mean (SD) years		**47.6 (14.8)**	**54.2 (13.6)**	**44.5 (12.9)**	**<0.001**	**42.7 (13.4)**	**47.6 (11.6)**	**<0.001**
Male		**562 (63%)**	**459 (70%)**	**356 (73%)**	**<0.001**	139 (70%)	127 (77%)	0.154
Meets mNY criteria for AS		**597 (67%)**	**499 (77%)**	**335 (69%)**	**<0.001**	139 (70%)	117 (70%)	0.895
HLA-B27 positive[+]		530 (77%)	375 (82%)	283 (79%)	0.179	126 (82%)	89 (79%)	0.533
Radiographic sacroiliitis*		**597 (82%)**	**499 (88%)**	**335 (85%)**	**0.003**	139 (85%)	117 (88%)	0.500
Inflammatory lesion on MRI[+]		**483 (81%)**	**299 (75%)**	**295 (88%)**	**<0.001**	109 (84%)	104 (90%)	0.127
Good response to NSAIDs		**614 (71%)**	**434 (70%)**	**266 (58%)**	**<0.001**	99 (53%)	99 (62%)	0.091
Elevated CRP**		**432 (50%)**	**324 (52%)**	**286 (62%)**	**<0.001**	119 (64%)	103 (65%)	0.877
Symptom duration, median (IQR) years		**18.5 (7.9 to 32.5)**	**27.3 (13.0 to 37.1)**	**15.1 (6.9 to 27.0)**	**<0.001**	13.2 (6.2 to 26.3)	18.0 (7.8 to 29.1)	0.096
BMI, mean (SD)		**27.5 (5.6)**	**28.6 (5.1)**	**27.1 (5.8)**	**<0.001**	26.6 (5.7)	28.2 (6.0)	**0.018**
Quintiles of Index of Multiple Deprivation	1, most deprived	**94 (11%)**	**83 (13%)**	**132 (27%)**	**<0.001 *****	57 (29%)	46 (28%)	0.365***
	2	**149 (17%)**	**98 (15%)**	**99 (20%)**		39 (20%)	38 (23%)	
	3	**188 (21%)**	**145 (22%)**	**102 (21%)**		31 (16%)	35 (21%)	
	4	**220 (25%)**	**177 (27%)**	**93 (19%)**		41 (21%)	31 (19%)	
	5, most affluent	**239 (27%)**	**149 (23%)**	**63 (13%)**		31 (16%)	16 (10%)	
Highest level of education	Secondary school	**219 (25%)**	**231 (36%)**	**199 (41%)**	**<0.001**	82 (42%)	78 (48%)	0.290
	Apprenticeship	**66 (7%)**	**65 (10%)**	**55 (11%)**		23 (12%)	25 (15%)	
	Further education college	**273 (31%)**	**211 (33%)**	**133 (28%)**		57 (29%)	42 (26%)	

					p-value			p-value
	University degree	**232 (26%)**	**99 (15%)**	**69 (14%)**		26 (13%)	12 (7%)	
	Further degree	**94 (11%)**	**41 (6%)**	**27 (6%)**		7 (4%)	7 (4%)	
Alcohol status	Current	**698 (79%)**	**494 (76%)**	**330 (68%)**	**<0.001**	17 (9%)	18 (11%)	0.444
	Ex	**114 (13%)**	**122 (19%)**	**113 (23%)**		53 (27%)	36 (22%)	
	Never	**67 (8%)**	**33 (5%)**	**42 (9%)**		126 (64%)	112 (67%)	
Number of comorbidities	0	**554 (63%)**	**318 (50%)**	**264 (54%)**	**<0.001 *****	111 (56%)	81 (49%)	0.279* **
	1	**228 (26%)**	**186 (29%)**	**152 (31%)**		58 (29%)	60 (36%)	
	2	**75 (9%)**	**87 (14%)**	**50 (10%)**		22 (11%)	18 (11%)	
	≥3	**24 (3%)**	**50 (8%)**	**23 (5%)**		8 (4%)	7 (4%)	
Medication in the past 6 months	NSAIDs	**667 (76%)**	**443 (69%)**	**381 (78%)**	**<0.001**	150 (75%)	132 (80%)	0.347
	DMARDs	95 (16%)	57 (13%)	43 (12%)	0.310	12 (9%)	16 (13%)	0.210

Data presented as mean (standard deviation), median (interquartile range), number (percentage). Comparisons used t-test for continuous variables, Chi-squared test for categorical variables. Bold text highlights significant differences.

[+]Not all current smokers provided information on smoking quantity. Not all variables have complete data, in particular: HLA-B27 status tested in 1773 and MRI results were available for 1606.

*Radiographic sacroiliitis defined as grade 2 or more bilaterally or grade 3 or greater unilaterally.

**Above upper normal limit.

***Non-parametric test for trend across ordered groups.

SD, standard deviation; IQR, interquartile range; mNY, modified New York criteria; BMI, body mass index.

Table 2. Differences in extra-axial manifestations and measures of disease severity according to smoking status and quantity. A selection of disease severity measures is shown here with other variables shown in supplementary table 2.

		Smoking status				Smoking quantity[+]		
		Never smoker (n=890)	Ex-smoker (n=652)	Current smoker (n=489)	P-value	Light smoker (n=199)	Heavy smoker (n=166)	P-value
Extra axial manifestations, n (%)	Uveitis	**241 (27%)**	**166 (26%)**	**76 (16%)**	**<0.001**	29 (15%)	30 (18%)	0.366
	IBD	87 (10%)	82 (13%)	47 (10%)	0.135	19 (10%)	12 (7%)	0.429
	Psoriasis	87 (10%)	77 (12%)	69 (14%)	0.058	24 (12%)	26 (16%)	0.319
	Peripheral arthritis	**358 (41%)**	**270 (43%)**	**166 (36%)**	**0.044**	66 (35%)	60 (38%)	0.665
	Dactylitis	75 (9%)	58 (9%)	36 (8%)	0.672	15 (8%)	14 (9%)	0.805
	Enthesitis	211 (24%)	156 (25%)	103 (22%)	0.546	44 (24%)	34 (21%)	0.615
Disease activity, median (IQR)	BASDAI	**4.3 (2.2 to 6.4)**	**4.9 (2.7 to 6.7)**	**6.1 (4.1 to 7.5)**	**<0.001**	6.1 (4.4 to 7.4)	6.4 (4.7 to 7.6)	0.403
	ASDAS[+]	**2.1 (1.3 to 2.9)**	**2.3 (1.5 to 3.0)**	**2.8 (2.1 to 3.4)**	**<0.001**	2.7 (2.1 to 3.4)	2.9 (2.3 to 3.6)	0.114
BASFI, median (IQR)		**3.4 (1.4 to 6.0)**	**5.0 (2.4 to 7.3)**	**5.9 (3.5 to 8.1)**	**<0.001**	**5.8 (3.7 to 7.9)**	**6.8 (4.9 to 8.3)**	**0.026**
ASQoL, median (IQR)		**6 (2 to 11)**	**8.5 (3 to 13)**	**12 (7 to 16)**	**<0.001**	12 (8 to 16)	13 (9 to 16)	0.373
Chalder Fatigue Scale, median (IQR)		**14 (11 to 19)**	**14 (11 to 18)**	**17 (11 to 21)**	**<0.001**	17 (12 to 21)	17 (12 to 20)	0.466
Sleep, median (IQR)		**9 (4 to 15)**	**10 (5 to 16)**	**13 (6 to 17)**	**<0.001**	12 (6 to 17)	14 (9 to 18)	0.057
HADS, median (IQR)	Anxiety	**6 (3 to 10)**	**7 (4 to 11)**	**10 (6 to 13)**	**<0.001**	10 (6 to 13)	10 (6 to 13)	0.555
	Depression	**4 (2 to 7)**	**5 (3 to 9)**	**8 (4 to 11)**	**<0.001**	8 (4 to 11)	8 (4 to 11)	0.623

Bold text highlights significant differences.

[+]Not all current smokers provided information on smoking quantity. 1596 patients had ASDAS.

IQR, interquartile range; BASDAI, Bath AS disease activity index; ASDAS, AS disease activity score; BASFI, Bath AS functional index; ASQoL, AS quality of life questionnaire; Sleep, Jenkins Sleep Evaluation Questionnaire; HADS, Hospital Anxiety and Depression Scale; IBD, inflammatory bowel disease.

		Never smokers	Ex-smokers	Current smokers	Ex-smokers	Current smokers
Table 3. Comparisons between current, ex- and never smokers using fully adjusted regression models. A selection of disease severity measures is shown here with other variables shown in supplementary table 3.						
Extra axial manifestations	Uveitis	Reference	0.97 (0.74 to 1.27)	**0.68 (0.49 to 0.94)**	Reference	**0.70 (0.50 to 0.99)**
	IBD	Reference	1.40 (0.96 to 2.03)	1.03 (0.66 to 1.61)	Reference	0.73 (0.47 to 1.14)
	Psoriasis	Reference	0.94 (0.64 to 1.37)	**1.56 (1.05 to 2.32)**	Reference	**1.66 (1.09 to 2.54)**
	Peripheral arthritis	Reference	0.93 (0.73 to 1.19)	0.82 (0.62 to 1.08)	Reference	0.88 (0.65 to 1.17)
	Dactylitis	Reference	1.07 (0.71 to 1.60)	1.08 (0.68 to 1.72)	Reference	1.02 (0.62 to 1.65)
	Enthesitis	Reference	1.05 (0.80 to 1.38)	0.89 (0.65 to 1.22)	Reference	0.85 (0.61 to 1.18)
Disease activity	BASDAI	Reference	**0.35 (0.08 to 0.62)**	0.94 (0.64 to 1.24)	Reference	**0.59 (0.27 to 0.91)**
	ASDAS	Reference	**0.14 (0.01 to 0.28)**	**0.46 (0.32 to 0.61)**	Reference	**0.32 (0.17 to 0.47)**
BASFI		Reference	**0.53 (0.24 to 0.82)**	1.30 (0.97 to 1.62)	Reference	0.77 (0.42 to 1.11)
ASQoL		Reference	**0.88 (0.30 to 1.47)**	**2.64 (1.98 to 3.29)**	Reference	**1.75 (1.06 to 2.44)**
Chalder Fatigue Scale		Reference	0.02 (-0.60 to 0.63)	**1.34 (0.66 to 2.02)**	Reference	**1.32 (0.60 to 2.05)**
Sleep		Reference	**0.72 (0.02 to 1.42)**	**1.89 (1.11 to 2.67)**	Reference	**1.17 (0.35 to 2.00)**
HADS	Anxiety	Reference	**0.75 (0.25 to 1.26)**	**1.86 (1.30 to 2.42)**	Reference	**1.11 (0.52 to 1.70)**
	Depression	Reference	**0.63 (0.19 to 1.06)**	**1.9 (1.41 to 2.38)**	Reference	**1.27 (0.75 to 1.79)**

Results shown as regression coefficients β (95%confidence interval) for disease severity markers and odds ratios (95%CI) for extra-axial manifestations. Bold text highlights significant coefficients and odds ratios.

BASDAI, Bath AS disease activity index; ASDAS, AS disease activity score; BASFI, Bath AS functional index; ASQoL, AS quality of life questionnaire; Sleep, Jenkins Sleep Evaluation Questionnaire; HADS, Hospital Anxiety and Depression Scale; IBD, inflammatory bowel disease.